IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s): Houghton, et al.	Confirmation No.: 3599
Application No.: 09/627,694	
Filed: 28 July 2000	Group Art Unit: 1642
Title: Method and Compositions for Stimulation of an Immune Response to Differentiation Antigen Induced by Altered Differentiation Antigen	Examiner: A. Harris
Attorney Docket No.: MSK.P-026-2	

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 4/22/2002. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is Sloan-Kettering Institute for Cancer Research.

Related Appeals and Interferences

There are no related appeals or interferences of which applicants are aware.

Status of Claims

Claims 31, 33-37 and 40 are pending in this application. Claims 1-30, 32, 38 and 39 have been cancelled without prejudice.

I hereby certify that this paper and any attachments named herein are being deposited with the US Postal Service as first-class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on February 28, 2003 by Marina T. Larson.

Marina T Larson

Signature

Claims 34-37 and 40 stand withdrawn from consideration pursuant to a restriction requirement mailed on March 1, 2001. A petition was filed on July 18, 2001 asserting that claims 34-37 and 40 should be the subject of only a species restriction requirement, since they are dependent on claim 31 which is generic. This petition was denied, but it was indicated that this issue should be revisited if the generic claim (claim 31) were found to be allowable. Accordingly, claims 34-37 and 40 have not been cancelled, pending the outcome of this appeal, but will not be addressed further herein.

Status of Amendments

The Preliminary Amendment filed on November 3, 2000 has been entered correcting the priority information. The Amendment filed on April 2, 2001 has been entered adding claim 40. The Amendment filed on January 4, 2002, has been entered as is reflected in the Appendix of claims on appeal.

Summary of Invention

The present application relates to insect cell lines that express a differentiation antigen derived from human melanocytes. Expression of the human protein in non-human cells results in subtle difference that allows the protein to serve as a therapeutic agent and to stimulate an immune response against the original antigen, even though the native protein is non-immunogenic in humans. Thus, immune response can be generated against melanoma in a treated individual using the products expressed by the cell lines. The elected species of melanoma differentiation antigen is gp75.

Issues on Appeal

The sole issue on Appeal is whether claims 31 and 33 are obvious in light of Houghton, et al. (Annals New York Academy of Sciences 690:59-38, August 12, 1993) in view of Ausubel et al. (Ausubel, F.M., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A., and Struhl, K., "Expression of Proteins in Insect Cells Using Baculoviral Vectors," *Current Protocols*

in Molecular Biology, Greene Publishing Associates and Wiley-Interscience, 1990, Vol. 2, 16.8.1-16.11.7).

Grouping of Claims

All claims are argued as a single group and stand or fall together.

Argument

Claims 31 and 33 stand rejected under 35 USC § 103(a) as being unpatentable over Houghton, et al. in view of Ausubel et al. In making a rejection under 35 USC § 103 in which references are combined, it is axiomatic that more is required than disclosure of the isolated pieces found in the claims. Indeed as observed in *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988), "'citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious." What is required is some teaching or suggestion supporting the argument that the combination should be made. *In re Fine*, 5 U.S.P.Q. 2d 1596 (Fed. Cir. 1988). Absent such a teaching or suggestion, there is no *prima facie* case of obviousness. Even where a *prima facie* case of obviousness is presented, however, an invention may still not be obvious if the combination when actually made has properties which could not reasonably be predicted in light of the art. In the present case, the Examiner has not established a *prima facie* case of obviousness, nor has the Examiner given proper credit to evidence of the properties of the claimed invention. This being the case, the rejection of the claims should be reversed.

The Examiner asserts that Houghton provides the basis that human gp75 can be expressed in a cell line, and that Ausubel teaches a baculoviral expression system transfected within insect cells to express proteins, and that therefore expressing human gp75 in insect cells would have been obvious. There is no suggestion in the references connecting the two in any way. Indeed, without the guidance of the present invention, nothing would direct the person skilled in the art to think of insect cell expression systems. Thus, the Examiner's argument is essentially that once a protein is cloned in one system, cloning in every other known system is per se obvious.

The total teaching of the Houghton reference on which the Examiner relies is a single sentence on Page 65, to whit: "The identity of these clones [including a full length open-reading frame clone] was confirmed by expressing gp75 cDNA in mouse L cells. " The purpose of the research described was to confirm that gp75 is a homologue of the mouse brown locus protein. Once this study was done and the result determined that the two proteins were homologous, there was no need to repeat the study, nor is there a suggestion of any other reason to make human gp75 in mouse L cells since the identity of the cone had already been confirmed. This being the case, there is plainly no suggestion (nor has the Examiner identified one) in Houghton to make any additional cell lines which express human gp75.

Ausubel is a manual of research techniques which includes a chapter on cloing in insect cells. The Examiner has asserted that Ausubel teaches a "great likelihood of obtaining biologically active products from such methods and host cells due to the baculovirus' efficient promoter strategy and the high infection rate of insect host cells." (Office Action of April 22, 2002, Page 3). What the reference actually teaches is a likelihood that **if** a protein is expressed, it will happen in a reasonable yield. Ausubel makes it clear that baculoviruses may not work for producing all proteins. On page 16.8.3, second column, towards the bottom, Ausubel provides as one of the steps for overproducing proteins using the baculoviral expression system: "5. Determine whether the potential recombinant viruses express the protein of interest." On page 16.11.3, first paragraph, Ausubel recommends that the recombinant virus be screened for its ability to produce the protein of interest, and that the screening should be individually tailored to the properties of the protein being overproduced and the availability of detection reagents. Ausubel does not contemplate that the baculovirus expression system will work for all proteins, and Ausubel recognizes that experimentation will be needed to determine whether a particular protein of interest could be produced using this system. Ausubel suggests ways to optimize for protein production if the protein production is possible using the system, but Ausubel provides no indication that insect cell lines would be expected to produce melanosomal proteins as discussed in Houghton.

Additionally, on page 16.11.5 under Determining Time Course of Maximum Protein Production Ausubel states that "because individual proteins display differences in their stability

in insect cells, it is recommended that the time course of protein accumulation be charted for each protein expressed using this system." This further emphasizes that baculoviruses would not be suitable for production of all proteins and that a significant amount of experimentation may be required to determine whether the baculovirus system would be suitable for production of a particular protein. Therefore, Applicants respectfully submit that, contrary to the Examiner's assertion, Ausubel does not teach a great likelihood of obtaining biologically active products, but rather teaches that the system may not work for all proteins and experimentation will be necessary to determine if the system will work for a particular protein.

The challenge of producing proteins like gp75 is not a trivial one. As a membrane bound glycoprotein, gp75 requires post-processing to acquire the characteristics of the native protein. Houghton mentions expression of human gp75 in mouse fibroblasts and cites to a reference that describes the use of methods as described in Bouchard (Exhibit A). Bouchard in turn describes expression of human tyrosinase cDNA in mouse fibroblasts. Although Bouchard concerns a different protein, it teaches concern about whether melanosomal proteins in general are expressable at all in mammalian cells which lack melanosomes. The Examiner has never stated how all of this is consistent with her assertion of a reasonable expectation of success.

What the Examiner has said is that one skilled in the art would have motivated to make insect cells to express gp75 with a reasonable expectation of success "because it is known in the art that sources of altered antigen can induce effective immune responses, such as tumor antigens." (Office Action of April 22, 2002, Pages 3-4) This is using Applicants' own invention against them with a vengeance. At no time has the Examiner provided a reference to support this statement, although it was challenged in both the interview and the Response after Final and despite the fact that the Examiner acknowledged at the interview that this assertion could not be maintained without a reference.

In the Advisory Action, the Examiner did not repeat the statement using Applicants' invention to justify the rejection, but instead made a new unsupported statement of "fact" namely "it is art known that the gp75 is a tumor rejection antigen with a high propensity to act as an effective immunogen." Facts of this sort simply cannot be advanced without support in the form of a reference or other evidence where the merits of the evidence can be challenged as

appropriate. *In re Ahlert*, 165 USPQ 418, 420-21 (CCPA 1970). This is especially true where the Examiner's assertion of what is well known is in direct contradiction of the specification under examination. The specification in this case states at Page 1, lines 21-22, that with respect to melanocyte differentiation antigens, "in most cases, the immune system of the individual is tolerant of these antigens, and fails to mount an effective immune response," and Example 1 shows that mice immunized with mouse gp75 did not produce autoantibodies to gp75 (Example 1, Page 9). Without some greater understanding of what the Examiner is trying to say is well known, Applicants cannot refute the correctness of the statement, or address its relevance in connection with the cited references.

For the foregoing reasons, Applicants submit that the Examiner has failed to make a *prima facie* case of obviousness. Even if this threshold has been met, however, the characteristics of the cell lines which are the subject of this invention could not have been predicted and therefore provide evidence that the invention is not obvious. Nothing in the references cited by the Examiner nor in the Examiner's arguments suggests that insect cells expressing human gp75 would make anything but the genuine article. In fact, however, there is something different about the protein made by these cells and this something leads to the unexpected result that the protein can be introduced into a tumor-bearing host to break the tolerance to the autoantigen and stimulate an immune response to the tumor. (See Example 3 of the present specification.)

In conclusion, Applicants assert that none of the references cited by the Examiner contain a suggestion or motivation for combining the teachings of the references. Ausubel is a basic reference teaching how insect cells may be used to express some, but clearly not any and all proteins. Houghton teaches only the expression of human gp75 in mouse cells for a limited experimental purpose. Houghton provides no motivation or suggestion to seek more efficient or different methods for preparing gp75. Ausubel provides no motivation or suggestion to modify the teaching of Houghton to use insect cells instead of mouse cells. Further, Ausubel provides no reasonable expectation that insect cell lines would be expected to produce melanosomal proteins. Finally, neither reference suggests that the human protein when produced in insect cells would be somehow different from the same protein when expressed in human cells, or that this difference

would allow the protein expressed in the insect cells to function to break the normal tolerance to melanosomal autoantigens.

For the foregoing reasons, Applicants submit that the rejection of claims 31 and 33 should be reversed, and that the case should be returned to the Examiner for consideration of unelected claims 34-37 and 40.

Respectfully submitted,

February 28, 2003
Date

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APPENDIX

CLAIMS ON APPEAL

31. (Amended) A non-human cell line expressing a human differentiation antigen, wherein the human differentiation antigen is derived from human melanocytes and wherein the cell line is an insect cell line.

33. The cell line of claim 31, wherein the human differentiation antigen is gp75.